In the first aspect, a segment of an HLA locus is PCR amplified using labeled primers that comprise HLA allele-specific DNA. Thus, amplification will occur only when the individual has the HLA alleles that correspond to the allele-specific primers. The amplification product is then hybridized to a locus-specific capture oligonucleotide. The sequence of the locus-specific oligonucleotide is carefully chosen to allow hybridization to sequences common to all the amplification products. That is, sequences defined as being allele-specific are not used as locus-specific capture oligonucleotides. The locus-specific capture oligonucleotides are immobilized on a solid surface. The labeled amplification products can be hybridized with the locus-specific capture oligonucleotide either before or after immobilization on a solid surface. Once the hybridization complex is immobilized, unincorporated labeled primers are removed and the labeled allele-specific complexes are detected, allowing identification of the individual's HLA genotype.

IV. Rejections under 35 U.S.C. §112, second paragraph

Claims 11 and 12 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Applicants previously elected the nucleic acid species of SEQ ID NO: 277. The Office Action alleges that SEQ ID NO: 277 is not contained in any HLA allele and thus SEQ ID NO: 277 cannot be used in the methods of the present application. Thus, claims 11 and 12 are allegedly indefinite for reciting SEQ ID NO:277.

Applicants respectfully traverse this rejection. Applicants assert that one of ordinary skill in the art would understand the claimed invention in light of the specification. "[35 U.S.C.] §112, second paragraph, requires a determination of whether those skilled in the art would understand what is claimed in light of the specification." *Orthokinetics v. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986).

The application clearly defines SEQ ID NO:277 as an HLA locus-specific class II capture oligonucleotides. (Specification at page 13, lines 8-17.) HLA locus-specific capture oligonucleotide is defined as a capture oligonucleotide that is complementary to and hybridizes to a conserved region of an HLA locus. (Specification

at page 9, lines 14-18.) Capture oligonucleotide is further defined as having the ability to bind to some or all of the sequences that can be generated by the amplification of HLA allele sequences using HLA allele-specific primers. (Specification at page 12, lines 27-30.) Thus, a capture oligonucleotide is not required to have an allele specific sequence, but rather is required to hybridize to an amplified product found between allele-specific primer sequences. Also by definition, locus-specific capture oligonucleotides possess sufficient complementarity to the amplified HLA sequences such that they can hybridize to an amplified sequence under stringent conditions. (Office Action at Page 24, line 35 continuing through page 25, line 1). Thus, the exact sequence of a locus-specific capture oligonucleotide, such as SEQ ID NO: 277, does not need to be found in an HLA locus or allele, so long as the locus-specific capture oligonucleotide will hybridize to the amplified HLA locus or allele of interest.

The specification does demonstrate that SEQ ID NO:277 hybridizes to sequences found at the class II HLA locus. In Example 3, Applicants used SEQ ID NO:277 as a positive control for PCR amplification of Class II HLA DNA sequences. (Specification at page 36, lines 1 and 23.) Applicants remind the Examiner that SEQ ID NO:277 was used as a positive control because, as a locus specific sequence, it provided a positive result with all tested allele-specific primers.

The Office Action also alleges that the specification does not disclose HLA alleles that can be captured with the SEQ ID NO:277 probe. Applicants respectfully point out that SEQ ID NO:277 is identified as an HLA locus-specific class II capture oligonucleotide and thus, hybridizes with sufficient complementarity to Class II HLA DNA sequences. (Specification at page 13, lines 8-17.) Thus, SEQ ID NO: 227 is properly defined as a capture oligonucleotide for use in the claimed methods.

In view of the above remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

V. Rejections under 35 U.S.C. §102(b)

Claims 1, 3, 4, 10, 14, and 15 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Kaneshige *et al.*, MHC & IRS Supplement to Vol. 1, 1994 pages 159-164. The Office action alleges that Kaneshige *et al.* teach a method of identifying an HLA genotype of an individual, comprising obtaining a sample of template nucleic acid from the individual; amplifying the template nucleic acid with HLA allele-specific primers; hybridizing the amplification products with HLA locus-specific capture oligonucleotides to form a detectable complex; and detecting the complex to identify the HLA genotype. As described below, the Office Action mischaracterizes the technique disclosed in Kaneshige *et al.*

Applicants respectfully traverse the rejection. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited references must contain every element of the claims at issue. Kaneshige *et al.* does not contain every element of the claimed invention.

The present invention is described in detail above. Briefly, the rejected claims are directed to a method of determining an individual's HLA genotype by PCR amplification using labeled allele-specific primers, followed by hybridization of the amplification product to an immobilized locus-specific oligonucleotide.

After amplification of an HLA allele-specific sequence, Kaneshige *et al.* teaches hybridization of the PCR amplification product to allele-specific SSOPs, not to locus-specific capture oligonucleotides as asserted by the Examiner. SSOP refers to sequence-specific oligonucleotide probes. The SSOPs were chosen to define the allele in each DRB1 allele group; thus, they are allele-specific. (Kaneshige *et al.* at page 162, column 1.) SSOPs are described as being able to detect a difference of a single base pair in allelic variation. (*Id.* at page 162, column 2.) As defined by Applicants, a locus-specific capture oligonucleotide will bind to all amplification products, and will not be

able to detect single base pair allelic variation. Kaneshige *et al.* does not disclose or teach hybridization of an HLA locus-specific capture oligonucleotide to a PCR amplification product. Thus, Kaneshige *et al.* does not disclose all the elements of the claimed invention and cannot anticipate the claims.

In view of the above remarks, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

V. Rejections under 35 U.S.C. §103(a)

Claims are rejected over Nevinney-Stickel *et al.* in view of Kaneshige *et al.*; over Bunce *et al.* in view of Morris *et al.*; over Kaneshige *et al.* in view of Allen *et al.* and Erlich *et al.*; over Erlich *et al.* in view of an alternately searched sequence; and over Bunce *et al.* in view of Morris *et al.*, Kaneshige *et al.*, Allen *et al.*, and Erlich *et al.*

In response, Applicants assert that the Examiner has not established a case of *prima facie* obviousness. To establish a case of *prima facie* obviousness, the Examiner must meet three basic criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). M.P.E.P. §§ 706.02(j) and 2143.

The references cited by the Examiner fail to provide a reasonable expectation of success in practicing the invention and fail to provide a motivation for the combination of the references. In addition, the references cited by the Examiner fail to provide all the elements of the rejected claims.

A. The claimed invention is not obvious over Nevinney-Stickel et al. in view of Kaneshige et al.

Claims 2, 3, 4, 5, 10, 14, and 15 are rejected as allegedly being obvious over Nevinney-Stickel *et al.* in view of Kaneshige *et al.*

Nevinney-Stickel *et al.* teach a method for identifying an HLA genotype of a subject. (Nevinney-Stickel *et al.*, *European Journal of Immunogenetics* 20:419-427 (1993)) Template DNA is first obtained from a subject and then amplified using two primers that flank and define a 271 base pair segment of the polymorphic second exon of the HLA-DRB locus, *e.g.*, not allele-specific primers. (Nevinney-Stickel *et al.* at page 421, first full paragraph.) The amplification products are then hybridized with a multitude of labeled primers that correspond to regions of allele specificity in DRB genes, *e.g.*, allele specific primers. (*Id.* at page 420, paragraph 3 and Table 1.) The hybridization complexes are then immobilized on a solid surface and detected. The disclosure of Kaneshige *et al.* is described above.

Applicants respectfully point out that the Office Action mischaracterizes the methods of Nevinney-Stickel *et al.* The reference teaches locus-specific primers for amplification of genomic DNA, not allele specific primers as asserted by the Office Action and as claimed by Applicants. (Office Action at page 6.) The reference further teaches hybridization of the amplification product to allele-specific capture oligonucleotides, not locus-specific oligonucleotides as asserted by the Office Action and as claimed by Applicants. (*Id.*)

Neither reference, alone or in combination, discloses or suggests using allele-specific primers for amplification of HLA DNA, followed by hybridization to locus-specific capture oligonucleotides as is claimed. Thus, the cited references do not teach all the elements of the claimed invention. In addition, the cited references fail to provide a motivation to combine or modify their teaching to arrive at the claimed invention.

B. The claimed invention is not obvious over Bunce et al. in view of Morris et al.

Claims 16-19, 22, 23, 25, and 26 are rejected as allegedly being obvious over Bunce *et al.* in view of Morris *et al.* Claims 16-28 have been canceled without prejudice to subsequent revival. In view of this amendment, the claimed invention is not obvious over Bunce *et al.* in view of Morris *et al.*

C. The claimed invention is not obvious over Kaneshige et al. in view of Allen et al. and Erlich et al.

Claim 11 is rejected as allegedly obvious over Kaneshige *et al.* in view of Allen et al. and Erlich *et al.* Claim 11 is directed to determining the HLA genotype of an individual using the claimed method with elected allele-specific primers SEQ ID NO:192 and SEQ ID NO:222.

The disclosure of Kaneshige *et al.* is described above. Kaneshige also discloses primer R86A, which allegedly comprises SEQ ID NO:222. Allen *et al.* teach a method for identifying an HLA genotype of a subject (Allen *et al.*, BioTechniques 19:454-463 (1995)). The Examiner alleges that Allen *et al.* teach an allele-specific primer that comprises SEQ ID NO:192.

Erlich *et al.* teach a method for identifying an HLA genotype of a subject. (Erlich *et al.*, *European Journal of Immunogenetics* 18:33-55 (1991)). Template DNA is first obtained from a subject and then amplified using labeled locus-specific primers. (Erlich *et al.* at page 35, third full paragraph.) The amplification products are then hybridized with a multitude of immobilized probes that correspond to regions of allele specificity in HLA genes, *e.g.*, allele-specific probes. (*Id.* at first paragraph.) The labeled amplification products are then detected. The Examiner alleges that the DNA sequence of SEQ ID NO:192 is comprised of sequences disclosed in Erlich *et al.* for alleles 1501, 1502, 1601, and 1602. The Examiner also alleges that the DNA sequence of SEQ ID NO:222 is comprised by complementary sequences disclosed in Erlich *et al.* for alleles 1601 and 1602. The Examiner further alleges that those of skill in the art would

have been motivated to modify the primers taught by Allen *et al.* and Erlich *et al.* in the methods of Kaneshige *et al.*

Applicants respectfully traverse the rejection. The cited references do not teach or suggest using allele-specific primers for amplification of HLA DNA, followed by hybridization to locus-specific capture oligonucleotides as is claimed. Thus, the cited references do not teach all the elements of the claimed invention. In addition, the cited references fail to provide a motivation to for their combination in the practice of the claimed invention.

D. The claimed invention is not obvious over Erlich et al.

Claims 12 and 13 are rejected as allegedly obvious over Erlich *et al.* The Examiner admits that the elected sequence, SEQ ID NO:277, is free of the prior art. However, the Examiner has improperly searched and examined an alternate sequence, SEQ ID NO:274.

The disclosure of Erlich *et al.* is described above. The Office Action mischaracterizes the HLA genotyping technique of Erlich *et al.* as including amplification of template DNA using two HLA allele specific primers and hybridizing the amplification products to HLA locus-specific capture oligonucleotides. As discussed above, Erlich *et al.* disclose only the use of locus-specific amplification primers and allele specific hybridization probes or capture alleles. Erlich *et al.* do not teach or suggest the claimed methods of using allele-specific amplification primers and locus-specific capture probes as is presently claimed.

The Office Action further alleges that SEQ ID NO:274 is contained in HLA DQB1 alleles disclosed in Erlich *et al.* As the methods disclosed in the reference do not teach or suggest the claimed methods, and as SEQ ID NO:274 is not an elected sequence, this allegation has no bearing on the patentability of the claims.

E. The claimed invention is not obvious over Bunce et al. in view of Morris et al., Kaneshige et al., Allen et al., and Erlich et al.

Claims 16-26 are rejected as allegedly being obvious over Bunce *et al.* in view of Morris *et al.*, Kaneshige *et al.*, Allen *et al.*, and Erlich *et al.* Claims 16-28 have been canceled without prejudice to subsequent revival. In view of this amendment, the claimed invention is not obvious over Bunce *et al.* in view of Morris *et al.*, Kaneshige *et al.*, Allen *et al.*, and Erlich *et al.*

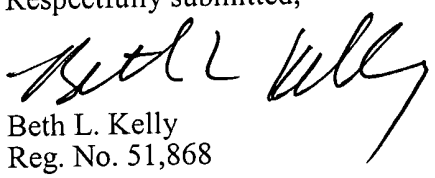
In view of the above amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, The Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

11. (Once amended) The method according to claim 1 or 2, wherein said HLA allele-specific forward primers and HLA allele-specific reverse primers are selected from the group consisting of:[selected from the group consisting of:]

SEQ ID NOS: 169-269.

16. (Cancelled) A method for identifying an HLA genotype of a subject, the method comprising:

(a) isolating template nucleic acid from a sample from said subject;

(b) immobilizing a plurality of HLA allele-specific reverse primers on a solid phase;

(c) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and said immobilized reverse HLA allele-specific reverse primers to form amplification products, wherein said forward primers comprise a detectable label; and

(d) detecting said amplification products to identify said HLA genotype of said subject.

17. (Cancelled) The method according to claim 16, wherein said template nucleic acid is cDNA or genomic DNA.

18. (Cancelled) The method according to claim 16, wherein said template nucleic acid is isolated from blood or cord blood.

19. (Cancelled) The method according to claim 16, wherein said solid phase is a member selected from the group consisting of: a bead, a chip, a microtiter plate, a polycarbonate microtiter plate, polystyrene microtiter plate, and a slide.

23. (Cancelled) The method according to claim 16, wherein said HLA genotype is a class II HLA genotype.

24. (As filed) The method according to claim 16, wherein said HLA allele-specific reverse primers and said HLA allele-specific forward primers are selected from the group consisting of:

SEQ ID NOS: 169-269.

25. (Cancelled) The method according to claim 16, wherein said detectable label comprises a member selected from the group consisting of:

radioactive moiety, a fluorescent moiety, a chemiluminescent moiety, an antigen, and a binding protein.

26. (Cancelled) The method of claim 25, wherein said fluorescent moiety is fluorescein or 5-(2'-aminoethyl) aminonaphtalene-1-sulfonic acid (EDANS).

28. (Cancelled) The method of claim 16, wherein said forward primers and said reverse primers are selected from the group consisting of :

SEQ ID NOS: 169-269.

APPENDIX B

CLAIMS UNDER EXAMINATION

1. (As filed) A method for identifying an HLA genotype of a subject, the method comprising:

(a) obtaining a sample comprising a template nucleic acid from said subject;

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form amplification products, wherein said forward primers or reverse primers comprise a detectable label;

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides immobilized on a solid phase to form a plurality of detectable complexes; and

(d) detecting said detectable complexes to identify said HLA genotype of said subject.

2. (As filed) A method for identifying an HLA genotype of a subject, the method comprising:

(a) obtaining a sample comprising a template nucleic acid from said subject;

(b) amplifying said template nucleic acid with a plurality of HLA allele-specific forward primers and HLA allele-specific reverse primers to form amplification products, wherein said forward primers or reverse primers comprise a detectable label;

(c) hybridizing said amplification products with a plurality of HLA locus-specific capture oligonucleotides to form a plurality of detectable complexes;

(d) immobilizing said detectable complexes on a solid phase; and

(e) detecting said detectable complexes to identify said HLA genotype of said subject.

3. (As filed) The method according to claim 1 or 2, wherein said template nucleic acid is isolated from blood or cord blood.

4. (As filed) The method according to claim 1 or 2, wherein said template nucleic acid is cDNA or genomic DNA.

5. (As filed) The method according to claim 1 or 2, wherein said solid phase is a member selected from the group consisting of: a bead, a chip, a microtiter plate, a polycarbonate microtiter plate, polystyrene microtiter plate, and a slide.

10. (As filed) The method according to claim 1 or 2, wherein said HLA genotype is a class II HLA genotype.

11. (Once amended) The method according to claim 1 or 2, wherein said HLA allele-specific forward primers and HLA allele-specific reverse primers are selected from the group consisting of:

SEQ ID NOS: 169-269.

12. (As filed) The method according to claim 1 or 2, wherein said locus-specific capture oligonucleotides are selected from the group consisting of:

SEQ ID NOS: 270-275.

13. (As filed) The method according to claim 12, wherein said capture oligonucleotides further comprise a 5' amine group or a 5'(T)5-20 oligonucleotide sequence.

14. (As filed) The method according to claim 1 or 2, wherein said detectable label comprises a member selected from the group consisting of:

radioactive moiety, a fluorescent moiety, a chemiluminescent moiety, an antigen, and a binding protein.

15. (As filed) The method of claim 14, wherein said fluorescent moiety is fluorescein or 5-(2'-aminoethyl) aminonaphtalene-1-sulfonic acid (EDANS).